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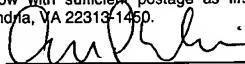


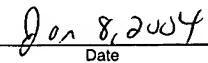
CASE LD0283 NP

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

BENIGNI ET AL.

APPLICATION NO: 10/668,032

FILED: SEPTEMBER 22, 2003

FOR: METHODS FOR THE PREPARATION, ISOLATION AND  
PURIFICATION OF EPOTHILONE B, AND X-RAY CRYSTAL  
STRUCTURES OF EPOTHILONE B

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INFORMATION DISCLOSURE STATEMENT

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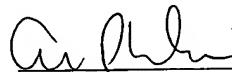
Applicants believe this paper is being filed before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required. If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-3880.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO-1449.

Copies of these references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO 1449 form(s).

Respectfully submitted,



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Date: 06/ 8, 2004



## FORM PTO-1449

## PATENT INFORMATION DISCLOSURE STATEMENT

Docket No.: LD0283 NP Sheet 1 of 6  
 Serial No.: 10/668,032 Group:  
 Applicant: Benigni et al.  
 Filing Date: September 22, 2003

## U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Sub-class	Filing Date
AA	08/856,533	5/14/97	Nicolaou, K., et al.			5/14/97
AB	08/923,869	9/4/97	Nicolaou, K., et al.			9/4/97
AC	60/032,864	12/13/96	Nicolaou, K., et al.			12/13/96
AD	6,194,181 B1	2/27/01	Hofmann, H., et al.			2/12/99
AE	6,204,388 B1	3/20/01	Danishefsky, S.J., et al.			2/24/99
AF	6,211,412 B1	4/3/01	Georg et al.			3/29/99
AG	6,242,469 B1	6/5/01	Danishefsky et al.			12/3/97
AH	6,316,630 B1	11/13/01	Danishefsky et al.			6/6/00
AI	6,369,234 B1	4/9/02	Danishefsky et al.			10/11/00
AJ	6,380,227 B1	9/7/00	Mutz			4/30/02

## FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Sub-class	Filing Date
BA	4138042.8	5/27/93	Germany (German and English abstract)			
BB	19639456.2	5/29/97	Germany (German and English translation)			
BC	19542986.9	5/29/97	Germany (German and English translation)			
BD	19636343.8	3/5/98	Germany (German and English abstract)			
BE	19645361.5	4/30/98	Germany (German and English abstract)			
BF	19645362.3	4/30/98	Germany (German and English abstract)			
BG	19647580.5	5/28/98	Germany (German and English translation)			
BH	19701758	7/23/98	Germany (German and English abstract)			
BI	19707505.3	9/3/98	Germany (German and English abstract)			
BJ	19713970	10/8/98	Germany (German and English abstract)			
BK	19720312	11/19/98	Germany (German and English abstract)			
BL	19821954	11/19/98	Germany (German and English abstract)			
BM	879 605	11/25/98	Europe (German and English abstract)			
BN	19726627	12/24/98	Germany (German and English abstract)			
BO	93/10121	5/27/93	World (PCT as published and English abstract)			
BP	97/19086	5/29/97	World (PCT as published and English translation)			
BQ	98/08849	3/5/98	World (PCT as published and English abstract)			
BR	98/22461	5/28/98	World (PCT as published and English translation)			
BS	98/24427	6/11/98	World			

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**FORM PTO-1449**  
**INFORMATION DISCLOSURE STATEMENT**

Docket No.: LD0283 NP Sheet 2 of 6  
 Serial No.: 10/668,032 Group:  
 Applicant: Benigni et al.  
 Filing Date: September 22, 2003

	BT	98/25929	6/18/98	World (PCT as published and priority documents: U.S. 60/032,864, 08/856,533, 08/923,869)			
	BU	98/38192	9/3/98	World (PCT as published and English abstract)			
	BV	98/47891	10/29/98	World (PCT as published and English abstract)			
	BW	99/01124	1/14/99	World			
	BX	99/03848	1/28/99	World (PCT as published and English abstract)			
	BY	99/07692	2/18/99	World (PCT as published and English translation)			
	BZ	99/39694	8/12/99	World (PCT as published)			
	BAA	99/42602	8/26/99	World (PCT as published)			
	BAB	99/43320	9/2/99	World (PCT as published)			
	BAC	00/37473	6/29/00	World (PCT as published)			
	BAD	00/00485	1/6/00	World (PCT as published and English translation)			
	BAE	00/66589	11/9/00	World (PCT as published)			
	BAF	99/43653	9/2/99	World (PCT as published)			
	BAG	99/02514	1/21/99	World (PCT as published)			
	BAH	00/31247	6/2/00	World (PCT as published)			
	BAI	00/49021	8/24/00	World (PCT as published)			
	BAJ	99/67252	12/20/99	World (PCT as published)			
	BAK	99/27890	6/10/99	World (PCT as published)			
	BAL	99/54319	10/28/99	World (PCT as published)			

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

	CA	Balog, A., et al., "Total Synthesis of (-)-Epothilone A", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 23/24, 2801-2803 (1996)
	CB	Bertini, F., et al., "Alkenes from Epoxides by Reductive Elimination with Magnesium Bromide-Magnesium Amalgam", <i>Chem. Commun.</i> , 144 (1970)
	CC	Bollag, D.M., et al., "Epothilones, A New Class of Microtubule-stabilizing Agents with a Taxol-like Mechanism of Action", <i>Cancer Res.</i> 55, No. 11, 2325-2333 (1995)
	CD	Fujisawa, T., et al., "Deoxygenation of Epoxides to Olefins with $\text{FeCl}_3 - n\text{-BuLi}$ System", <i>Chem. Lett.</i> , 883-886 (1974)

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FORM PTO-1449  
**INFORMATION DISCLOSURE STATEMENT**

Docket No.: LD0283 NP Sheet 3 of 6  
Serial No.: 10/668,032 Group:  
Applicant: Benigni et al.  
Filing Date: September 22, 2003

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)**

	CE	Fujiwara, Y., et al., "Reductive Coupling of Carbonyl Compounds to Olefins by Tungsten Hexachloride-Lithium Aluminum Hydride and Some Tungsten and Molybdenum Carbonyls", <i>J. Org. Chem.</i> , Vol. 43, No. 12, 2477-2479 (1978)
	CF	Gladysz, J. A., et al., "Deoxygenation of Epoxides by Metal Atom Cocondensation", <i>J. Org. Chem.</i> , Vol. 41, No. 22, 3647-3648 (1976)
	CG	Hofle, G., et al., "Epothilone A and B - Novel 16-Membered Macrolides with Cytotoxic Activity: Isolation, Crystal Structure, and Conformation in Solution", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 13/14, 1567-1569 (1996)
	CH	Hofle, G., et al., "N-Oxidation of Epothilone A-C and O-Acyl Rearrangement to C-19 and C-21-Substituted Epothilones", <i>Angew. Chem. Int. Ed.</i> , Vol. 38, No. 13/14, 1971-1974 (1999)
	CI	Inokuchi, T., et al., "Opening of Epoxides to Olefins or Halohydrins with Vanadium(II)-Tetrahydrofuran or Vanadium(III)-Tetrahydrofuran Complexes", <i>Synlett</i> , No. 6, 510-512 (1992)
	CJ	Kowalski, R. J., et al., "Activities of the Microtubule-stabilizing Agents Epothilones A and B with Purified Tubulin and in Cells Resistant to Paclitaxel (Taxol®)", <i>J. Biol. Chem.</i> , Vol. 272, No. 4, 2534-2541 (1997)
	CK	Kupchan, S. M., et al., "Reductive Elimination of Epoxides to Olefins with Zinc-Copper Couple", <i>J. Org. Chem.</i> , Vol. 36, No. 9, 1187-1190 (1971)
	CL	Martin, M. G., et al., "Epoxides as Alkene Protecting Groups. A Mild and Efficient Deoxygenation", <i>Tetrahedron Letters</i> , Vol. 25, No. 3, 251-254 (1984)
	CM	McMurry, J. E., et al., "Reduction of Epoxides to Olefins with Low Valent Titanium", <i>J. Org. Chem.</i> , Vol. 40, No. 17, 2555-2556 (1975)
	CN	McMurry, J. E., et al., "Some Deoxygenation Reactions with Low-Valent Titanium ( $TiCl_3/LiAlH_4$ )", <i>J. Org. Chem.</i> , Vol. 43, No. 17, 3249-3254 (1978)
	CO	Meng, D., et al., "Remote Effects in Macrolide Formation Through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 11, 2733-2734 (1997)
	CP	Nicolaou, K. C., et al., "An Approach to Epothilones Based on Olefin Metathesis", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 35, No. 20, 2399-2401 (1996)
	CQ	Nicolaou, K. C., et al., "Total Synthesis of Epothilone A: The Macrolactonization Approach", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 5, 525-527 (1997)
	CR	Nicolaou, K. C., et al., "Designed Epothilones: Combinatorial Synthesis, Tubulin Assembly Properties, and Cytotoxic Action against Taxol-Resistant Tumor Cells", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 19, 2097-2103 (1997)
	CS	Nicolaou, K.C., et al., "The Olefin Metathesis Approach to Epothilone A and Its Analogues", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 34, 7960-7973 (1997)
	CT	Nicolaou, K. C., et al., "Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 34, 7974-7991 (1997)

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**FORM PTO-1449**  
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Docket No.: LD0283 NP Sheet 4 of 6  
 Serial No.: 10/668,032 Group:  
 Applicant: Benigni et al.  
 Filing Date: September 22, 2003

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)**

	CU	Nicolaou, K. C., et al., "Synthesis of Epothilones A and B in Solid and Solution Phase", <i>Nature</i> , Vol. 387, 268-272 (1997)
	CV	Nicolaou, K. C., et al., "Synthesis of Epothilones A and B in Solid and Solution Phase" (Correction to <i>Nature</i> 387, 268-272 (1997)), <i>Nature</i> , 390, 100 (1997)
	CW	Raucher, S., et al., "Total Synthesis of (+)-Dihydrocostunolide via Tandem Cope-Claisen Rearrangement", <i>J. Org. Chem.</i> , Vol. 51, No. 26, 5503-5505 (1986)
	CX	Sato, M., et al., "Reduction of Organic Compounds with Low-Valent Niobium (NbCl <sub>5</sub> /NaAlH <sub>4</sub> )", <i>Chem. Letters</i> , 157-160 (1982)
	CY	Schinzer, D., et al., "Total Synthesis of (-)-Epothilone A", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 5, 523-524 (1997)
	CZ	Schobert, R., et al., "Reduction and Isomerization of Oxiranes and $\alpha$ -Diazoketones by Various Early Transition Metalloccenes", <i>Synlett</i> , Vol. 8, 465-466 (1990)
	CAA	Sharpless, K. B., et al., "Lower Valence Tungsten Halides. A New Class of Reagents for Deoxygenation of Organic Molecules", <i>J. Amer. Chem. Soc.</i> , Vol. 94, No. 18, 6538-6540 (1972)
	CAB	Su, D.-S., et al., "Total Synthesis of (-)-Epothilone B: An Extension of the Suzuki Coupling Method and Insights into Structure-Activity Relationships of the Epothilones", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 7, 757-759 (1997)
	CAC	Su, D.-S., et al., "Structure-Activity Relationships of the Epothilones and the First In Vivo Comparison with Paclitaxel", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 19, 2093-2096 (1997)
	CAD	Victory, S. F., et al., "Relative Stereochemistry and Solution Conformation of the Novel Paclitaxel-Like Antimitotic Agent Epothilone A", <i>Bioorg. Med. Chem. Lett.</i> , Vol. 6, No. 7, 893-898 (1996)
	CAE	Winkler, J. D., et al., "A Model For The Taxol (Paclitaxel)/Epothilone Pharmacophore", <i>Bioorg. Med. Chem. Lett.</i> , Vol. 6, No. 24, 2963-2966 (1996)
	CAF	Yang, Z., et al., "Total Synthesis of Epothilone A: The Olefin Metathesis Approach", <i>Angew. Chem. Int. Ed. Engl.</i> , Vol. 36, No. 1/2, 166-168 (1997)
	CAG	Bollag, D., et al., "Epothilone, A New Structural Class of Microtubule Stabilizer", Abstract, <i>Proc. Am. Assoc. Cancer Res.</i> , Vol. 36, 86 Meet. 454 (1995)
	CAH	Bollag, D., "Epothilones: Novel Microtubule-Stabilising Agents", <i>Expert Opin. Invest. Drugs</i> , Vol. 6, No. 7, 867-873 (1997)
	CAI	Bertinato, P., et al., "Studies Toward a Synthesis of Epothilone A: Stereocontrolled Assembly of the Acyl Region and Models for Macrocyclization", <i>J. Org. Chem.</i> , Vol. 61, No. 23, 8000-8001 (1996)
	CAJ	<i>Chemical &amp; Engineering News</i> , "Epothilone Epiphany: Total Syntheses", Vol. 74, No. 52, 24-26 (1996)
	CAK	<i>Chemical &amp; Engineering News</i> , "First Total Synthesis of Epothilone B", Vol. 75, No. 13, 23 (1997)

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Docket No.: LD0283 NP Sheet 5 of 6  
Serial No.: 10/668,032 Group:  
Applicant: Benigni et al.  
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**OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)**

	CAL	Chemical & Engineering News, "Solid-Phase Epothilone Synthesis Used to Create Analog Library", Vol. 75, No. 20, 33 (1997)
	CAM	Claus, E., et al., "Synthesis of the C1-C9 Segment of Epothilons", <i>Tetrahedron Lett.</i> , Vol. 38, No. 8, 1359-1362 (1997)
	CAN	De Brabander, J., et al., "Towards a Synthesis of Epothilone A: Rapid Assembly of the C1-C6 and C7-C12 Fragments", <i>Synlett</i> , Vol. 7, 824-826 (1997)
	CAO	Gabriel, T. and Wessjohann, L., "The Chromium-Reformatsky Reaction: Asymmetric Synthesis of the Aldol Fragment of the Cytotoxic Epothilons from 3-(2-Bromoacetyl)-2-Oxazolidinones", <i>Tetrahedron Lett.</i> , Vol. 38, No. 8, 1363-1366 (1997)
	CAP	Gerth, K., et al., "Epothilons A and B: Antifungal and Cytotoxic Compounds from <i>Sorangium cellulosum</i> (Myxobacteria) Production, Physico-chemical and Biological Properties", <i>J. Antibiotics</i> , Vol. 49, No. 6, 560-563 (1996)
	CAQ	Marshall, A., "Total Synthesis of Epothilone", <i>Nature Biotechnology</i> , Vol. 15, No. 3, 205 (1997)
	CAR	Meng, D., et al., "Studies Toward a Synthesis of Epothilone A: Use of Hydroxypyran Templates for the Management of Acyclic Stereochemical Relationships", <i>J. Org. Chem.</i> , Vol. 61, No. 23, 7998-7999 (1996)
	CAS	Meng, D., et al., "Total Syntheses of Epothilones A and B", <i>J. Am. Chem. Soc.</i> , Vol. 119, No. 42, 10073-10092 (1997)
	CAT	Menschling, S. and Kalesse, M., "Generation of Thiazoles by Column Dehydrogenation of Thiazolidines with MnO <sub>2</sub> ", <i>J. Prakt. Chem.</i> , Vol. 339, No. 1, 96-97 (1997)
	CAU	Mulzer, J. and Mantoulidis, A., "Synthesis of the C(1)-C(9) Segment of the Cytotoxic Macrolides Epothilone A and B", <i>Tetrahedron Lett.</i> , Vol. 37, No. 51, 9179-9182 (1996)
	CAV	Nicolaou, K., et al., "Chemistry, Biology and Medicine of Selected Tubulin Polymerizing Agents", <i>Pure Appl. Chem.</i> , Vol. 71, No. 6, 989-997 (1999)
	CAW	Nicolaou, K., et al., "Total Synthesis of Epothilone E and Related Side-chain Modified Analogues Via a Stille Coupling Based Strategy", <i>Bioorg. Med. Chem.</i> , Vol. 7, No. 5, 665-697 (1999)
	CAX	Schinzer, D., et al., "Studies Towards the Total Synthesis of Epothilones: Asymmetric Synthesis of the Key Fragments", <i>Chem. Eur. J.</i> , Vol. 2, No. 22, 1477-1482 (1996)
	CAY	Taylor, R. and Haley, J., "Towards the Synthesis of Epothilone A: Enantioselective Preparation of the Thiazole Sidechain and Macrocyclic Ring Closure", <i>Tetrahedron Lett.</i> , Vol. 38, No. 12, 2061-2064 (1997)
	CAZ	Schinzer, D., et al., "Syntheses of (-)-Epothilone A", <i>Chem. Eur. J.</i> , Vol. 5, No. 9, 2483-2491 (1999)
	CBA	Schinzer, D., et al., "Syntheses of (-)-Epothilone B", <i>Chem. Eur. J.</i> , Vol. 5, No. 9, 2492-2500 (1999)

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FORM PTO-1449  
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Serial No.: 10/668,032 Group:  
Applicant: Benigni et al.  
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**OTHER (Including Author, Title, Date, Pertinent Pages, etc.) (Continued)**

	CBB	Nicolaou, K. C., et al., "Synthesis and Biological Properties of C12,13-Cyclopropylepothilone A and Related Epothilones", <i>Chemistry &amp; Biology</i> , Vol. 5, No. 7, 365-372 (1998)
	CBC	Altmann, K.H., et al., "Epothilones and Related Structures – A New Class of Microtubule Inhibitors With Patent In Vivo Antitumor Activity," <i>Biochim. Biophys Acta</i> , 1470 (2000)
	CBD	Nicolaou et al., "Total Synthesis of Epothilone E and Analogs with Modified Side Chains Through The Stille Coupling Reaction", <i>Angew. Chem. Int. Ed.</i> 37, 84-87 (1998)
	CBE	Nicolaou et al., "Total Synthesis of Oxazole- and Cyclopropane-Containing Epothilone B Analogues by the Macrolactonization Approach", <i>Chemistry, European Journal</i> , Vol. 3, No. 12, 1971-1986 (1997)
	CBF	Nicolaou et al., "Chemical Biology of Epothilones", <i>Angew. Chem. Int. Ed.</i> , 37, 2014-2045 (1988)

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